

Antibiotic use monitoring in feedlots and dairies: Eight key concepts to help you guide your clients

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Abstract

Antibiotic use monitoring suffers from a lack of uniformity in the metrics used and the related terminology. There are 8 key concepts which can help guide veterinarians through the initial steps of deciphering antibiotic use data. First, there is no one perfect metric. It is also critically important to understand the granularity of the data from which the antibiotic use is calculated. Weight of antibiotics is confounded by different potencies. Regimens can help normalize antibiotic use, but be sure to know the difference between a documented regimen and estimated defined daily doses (DDD) and Defined Course Doses (DCDs). When using the number of reported regimens or estimated number of animals exposed as a proxy for disease incidence, be sure to understand how multiple exposures for the same disease incident were addressed. Kilograms of product sold for each food animal species has a unique relationship to the production cycle and time at risk for antibiotic use. Duration of antibiotic administration may be quite different from the duration of therapeutic effect and the duration of selection for antibiotic resistant bacteria. And, lastly, comparison of antibiotic use between food animal species by any antibiotic use metric is poorly advised.

Key words: antibiotics, monitoring, concepts

Introduction

Publications reporting antibiotic use in 22 US beef feedlots and 29 US dairies are expected to be published in 4th quarter 2020, along with papers reporting antibiotic use in US pork and poultry systems. The reporting of data and in-depth discussion of the metrics used are left to these publications. Rather, these proceedings review some basic concepts of interpreting antibiotic use metrics and the applications of these metrics by veterinary practitioners and their clients in supporting antibiotic stewardship.

The author has spent the last 5 years studying the application of antibiotic use metrics both globally and within the United States. Frankly, many of the nuances of the different metrics continue to require intense concentration to allow interpretation of the similarities and differences of often similar sounding terms. A new language has been created and sometimes weaponized in political arenas and domestic/international trade competition.

To further complicate the issue, some of the terms are calculated differently in the early literature, resulting in different values for the same term. And, on the same comparative chart we may see “use statistics” calculated by different methods, creating the classic apples vs oranges scenario.

With these issues in mind, please consider these key baseline concepts to help your clients interpret antibiotic use reports, starting with the 2 most foundational concepts for antibiotic use metrics. As a veterinarian, you will need to become a student of the antibiotic use metrics which will have an impact on your clients.

Antibiotic use Metric Concepts

1. There is no perfect metric.

Each metric which may be used to describe antibiotic use requires interpretation in light of how it was derived. Even more important is that the same metric applied across different production systems may need to be interpreted differently. Knowledge of and use of several metrics may be necessary to understand antibiotic use. This is not a new concept to veterinarians working in agriculture; we would rarely use a single metric to evaluate production and health for a client.

Metric numerators describe antibiotic use; considerations for *total antibiotic weight* and *regimens* are discussed below. In contrast, metric denominators are tasked with putting the antibiotic use in the context of some type of production or a combination of number of animals and time; considerations for the denominators *weight animals or product sold* and *animal years* are discussed below.

Published analyses of various antibiotic use metrics highlight many differences between the metrics. A study of veal farms in Belgium found that the farms changed in their antibiotic use rank depending on the metric used.⁶ Similarly, the effects of choice of metric and standardized values on the calculation of antibiotic use indicators in feedlots have been described.²

A lack of standardization, which results in poor transparency and comparability between data sources, has been described for both human and veterinary medicine.³ The nuances of differences in published metrics are beyond the scope of these proceedings, but the nuances do matter and veterinarians are going to be increasingly responsible for interpreting these metrics for their clients. The selection of the appropriate antimicrobial use metric should be done in

the context of the intended use of the data, demonstrating a second key concept vital to interpreting antibiotic use data...

2. Granularity really, really matters.

Antibiotic use data may be based on national sales data, production unit-level sales or total use data, or actual use data recorded at the individual animal or group level. In the case of individual animal or group records, the total antibiotic use is built from the individual record up; the milligrams of antibiotics and the regimens aren't estimated, they are described.

When using sales data for an individual production unit, reported regimens (such as those in treatment protocols) are used to estimate the number of animals exposed to an individual treatment, or the duration of exposure for a group. We lose some defining characteristics of the variation in actual regimens, but would be reasonably accurate in estimating the central tendencies of overall use.

National sales data require that the estimated average regimen and average weight at the time of treatment be estimated to convert these data to the number of animals exposed and the duration of their exposure; more assumptions and estimates are needed. A comparison between the Netherlands and Denmark confirmed that characterization of antibiotic use by combining national sales data with a population correction unit (PCU) caused the difference in use between the countries to be overestimated when compared to data collected from mandated national collection programs.¹

If the goal is to support antimicrobial stewardship at the individual production unit level, then nothing is worthy of our efforts other than the most granular data available; however, this is also typically the most labor-intensive data to collect. If a national policy based on gross reduction in weight of antibiotics is the goal, then national sales data serves the purpose as a measurement, although this source does little to inform decisions about use at the production unit level.

While the most granular antibiotic use data allow us to ask the most reasonable and detailed questions, the answers may not be there without detailed investigation at the user level.

3. Antibiotic use metrics often report the weight of drug administered, which is confounded by potency.

The basic answer to "how much" antibiotic often comes in the form of weight of antibiotic administered. In the case of antibiotics, the milligrams of an antibiotic required for activity against a pathogen in a diseased animal is typically not equivalent to the amount required for another antibiotic. This is obvious between antibiotic classes, but even within antibiotic classes the difference can be dramatic. For example, the dose of tulathromycin for bovine respiratory disease (BRD) is 2.5 mg/kg while the high label dose for tilmicosin is 20 mg/kg, an 800% difference. Differences between antibiotic groups can be even greater; the difference between

BRD label doses for tulathromycin (2.5 mg/kg) and florfenicol (40 mg/kg) is 1600%.

Why then do we use weight as a basis for antibiotic use measurement? Because it is the easiest to capture from less granular data and also because it satisfies the need for an 'amount'. If used in a system where differences in antibiotic use between different production sites are investigated as to why they occurred, and the effect of different antibiotic potencies is considered, then the underlying issues related to antibiotic stewardship can be discerned. If simply used as a policy or marketing stick, the shortcomings of measuring antibiotic use by total weight are obvious.

4. The "potency problem" of measuring use by weight of drug is commonly dealt with by conversion to estimated regimens or estimated days of exposure.

We have a way of normalizing milligrams of antibiotics used; we can calculate estimated use regimens. A regimen is a dose, route, frequency, and total number of administrations of an antibiotic. Assuming that the regimen of one antibiotic has the same period of efficacy or resistance selection as another antibiotic is an over-simplification of a complicated issue.

We have to be very careful as to what is defined as a regimen. Referencing principle #2 above, knowing from whence a reported regimen came is very important. If regimens come from detailed records indicating the number of animals receiving a regimen, that is the best we can do.

If the estimate of the number of animals exposed is from dividing the total weight of antibiotics by a value such as a Defined Course Dose (DCD), then both the number of animals exposed and the nature of that exposure are approximations; dose, route, duration, and frequency are estimates over the population. We should not confuse the number of defined course doses (nDCD) with a number of reported regimens. A defined course dose (DCD, note there is no 'n' in front) is an estimate of the number of antibiotic milligrams included in a standard course of therapy. Values for Defined Course Doses for veterinary applications (DCDvet) have been defined by bodies such as the European Medicines Agency (EMA).⁴ These terms have been used for an extended period in human medicine, with guidelines for assigning defined doses published by the World Health Organization (WHO) in 1991.⁷ Understand that the accuracy of the dose definition when compared to granular use data may differ drastically across livestock systems and specific antibiotics. For example, for some antibiotic uses the estimate of the most likely regimen can be easily and accurately defined (i.e. dry cow treatments). For other uses, such as CTC in beef cattle, the true regimen is variable (350 mg/hd/day for an unlimited duration vs 10mg/lb daily for a maximum of 5 days). Therefore, the reported nDCD for dry cow therapy on an individual farm is often reasonably representative of reality, while the reported nDCD of CTC use may have a more variable relationship with actual use depending on the regimen used.

An alternative to estimating regimens is estimating the number of days of exposure to an antibiotic. These estimates, known as defined daily doses (DDD), are commonly used for describing antimicrobial use. They suffer from all the challenges described for defined course doses. It is well characterized in the literature that data such as the amount of drug prescribed (the Prescribed Daily Dose, PDD) and the amount of drug actually used (the Used Daily Dose, UDD) can be quite different from the DDD.^{5,6}

5. Regimens, or animals exposed, reported by disease may serve as a proxy for disease incidence but be careful to understand the number of regimens or exposures per disease occurrence.

Even in very granular data, it is necessary to separate first treatments for a disease from subsequent treatments to avoid multiple counts of the same disease incident. Animal exposures calculated by dividing total use by a defined course dose may not be attributed to a specific disease, and also may capture multiple administrations for the same disease incident without the ability to discern this situation. The further we get from actual antibiotic use numbers in defined populations the closer we get to the antibiotic use monitoring equivalent of pseudoreplication in statistics.

6. The denominators consisting of weight of animal or product sold have a varying relationship with the duration of the production period for each animal and the proportion of the period each animal is at risk for antibiotic use.

This is a key concept for those wishing to compare antibiotic use between different types of production systems, especially for different food animal species. In beef feedlots, a finished steer could have been in the feedlot for close to a year in the case of a calf-fed Holstein or for as little as 120 to 140 days for a heavy yearling. Therefore, an animal year might represent one Holstein steer or up to 3 heavy yearling steers; the resulting liveweight kg sold per year would represent one Holstein steer and 3 heavy yearling steers, respectively. There are an infinite number of variations which could occur between these extremes. Each species has their unique set of characteristics related to the production period, and therefore...

7. Comparing antibiotic use between species by any metric is poorly advised.

Think of the life span of a chicken vs a pig vs a feedlot steer vs a dairy cow; these are not only different species but entirely different production systems. These species also have different periods of heightened risk for disease during their production lifespans. It is the denominators that most challenge us in normalizing antibiotic use metrics between species. We are best served by antibiotic monitoring efforts in each species applying a uniform method of antibiotic use monitoring across the various production systems coupled with knowledgeable veterinarians and producers interpret-

ing the metric values within the context of how they were generated.

8. Duration of antibiotic administration may be quite different from duration of therapeutic effect and duration of selection for antibiotic resistant bacterial populations.

The subject of this concept is incredibly complex. Suffice it to say that evaluating duration of exposure of one antibiotic or antibiotic class in relation to duration of exposure for another antibiotic is fraught with peril. This is another example of comparing apples and oranges.

The author also has reservations about applying durations of effect to single injection antibiotics for the purposes of calculating days of exposure. A troubling trend is to equate an estimated duration of therapeutic effect with the duration of selection pressure on both pathogen and commensal bacterial populations. This is the same superficial thinking that gets us into trouble with equating a “narrow spectrum” antibiotic with being “safer” in relation to selection for antibiotic resistance. Also, the concept that “low and long” concentrations are more problematic for antibiotic resistance selection pressure than are “short and high” concentrations is dangerous and oversimplified. A basic tenet of having respect for the complex nature of these issues is that both efficacy and selection for antibiotic resistance are dependent on the interaction of the antibiotic with a complex bacterial population, not just on the characteristics of the antibiotic alone.

The answer to these issues, in the author’s opinion, is to understand the limitations of the granularity of the data being reported and what may be extrapolated from these data. The data are what they are, and our responsibility is to limit attribution of effects and outcomes to those which have been demonstrated through rational investigation. Unfortunately, the data relating changes in regimens to changes in magnitude and duration of selection for resistant bacteria is sparse for the regimens we use in food animal production medicine.

Conclusion

Regardless of the complicated nature of quantifying how we use antibiotics, please stay engaged. We should anticipate benchmarking systems in the future where your clients will be compared to other producers. You, as a veterinarian prescribing these valuable tools and working with your clients to guide antibiotic use, are the pathway to antibiotic use monitoring which contributes to antibiotic stewardship. Without your interactions with your clients, and your boots on the ground to compare reality to the measured use, it is all just posturing and marketing.

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